UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/776,044	02/26/1997	MARGARET BYWATER	1614-178P	1463

2292 7590 02/24/2005

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
YU, MISOOK	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/776,044	BYWATER ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2004 and 23 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,10 and 16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/23/2004, and 11/23/2004 has been entered.

Claims 1-7, 9, 10, and 16-20 are pending and examined on merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office action contains new grounds of rejection.

Claim Rejections - 35 USC § 112, Withdrawn

The rejection of claim under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102, Moot

The rejection under 35 U.S.C. 102(e) as being anticipated by Vogelstein et al (US PAT 5,527,676; issued June 18, 1996; effective filing date of December 6, 1989) is moot because applicant cancelled the claim.

Claim Rejections - 35 USC § 103, Withdrawn

The rejection of claims under 35 U.S.C. 103(a) as being unpatentable over Vogelstein et al as applied to claim 15 above, and in view of Elledge et al (Breast

Cancer Res. Treat. 27, 95-102, 1993), and of Callahan (J. Natl. Cancer Institute, 83, 826-7, 1992) and further in view of Hedrum (IDS, BioTechniques, 17, 118-29, 1993) is withdrawn because of the amendment.

The Following Are the New Grounds of Rejection

Claim Rejections - 35 USC § 103

Claims 1-7, 9, and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allred et al., J Natl Cancer Inst. 1993 Feb 3;85(3):200-6 in view of US 5527676 A of record (the effective filing date of 1989).

The claimed invention is interpreted as drawn to method for prognostication of recurrence of breast cancer and providing guidance for treating breast cancer based on status of p53 mutation along with node status (base claim 1 and all dependent claim), as drawn to method for prognostication of cancer based on status of p53 mutation (base claim 3 and all dependent claims), wherein the p53 is mutation is detected by analyzing the p53 nucleotide sequences, wherein specific mutations are listed in claims 19, and 20.

Allred et al., teach both that p53 mutations and node status in breast cancer patients are prognostic indicators of "high tumor proliferation rate, early disease recurrence, and early death in node-negative breast cancer, both factors were independently associated with poor prognosis" (note the abstract). Based on the clinical studies of 700 breast cancers from axillary lymph node-negative patients, the authors of the study provides the treatment guidance by concluding that p53 mutational test, "when combined with other prognostic factors, may enhance our ability to identify node-

negative breast cancer patients at high risk for early disease recurrence and/or death, for whom the use of adjuvant chemotherapy is unequivocally justified" (note the conclusion section of the abstract).

Allred et al., do not teach the limitation of the instant base claims 1, ad 3 of determining a nucleotide sequence of exons 2-11 or analyzing the nucleotide sequence in exons 2-11, and whether the mutation as a missense, a deletion, or an insertion as claimed in instant claim 2, the conserved regions I-V, mutations in the conserved regions are bad prognosis as compared to the outside conserved region mutations

However, the '676 patent of record teach determining a nucleotide sequence of exons 2-11 (note Fig. 7 for the 11 exons of p53) or analyzing the nucleotide sequence in exons 2-11 (note columns 6, 9 13, 14, Fig. 8), total 20 point mutations 19 missense, 1 frame-shift" (note column 16, lines 61-63), as disclosed at Fig 8, and Table 1, also discloses that "the mutations tended to be clustered in four hotspots which accounted for 86% of the 21 missense mutations (5 mutations in region A, codons 132-143; five mutations in region B, codons 174-179; 3 mutations in region C, codons 236-248; 5 mutations in region D, codons 272-281)...Interestingly, the four hotspots for in vivo mutation coincided exactly with the four most highly conserved regions of the p53 gene, previously identified (Soussi, et al., Oncogene, vol. 1, p. 71, 1987). Of the 41 amino acids contained within regions A-D, 93% are identical in the wild-type p53 genes of amphibian, avian, and mammalian species, compared to a conservation of only 51-57% over the entire p53 coding sequence. The clustering of mutations and evolutionary conservation of regions A-D suggest that they play a particularly important role in

mediating the normal function of the p53 gene product." Note the last paragraph at columns 16-19. The various missense mutations in Table 1 include Arg to Cys substitution at codon 273 as claimed in the instant claim 20. The patent also discloses at column 5 lines 38-61. Instant specification at Fig. 1 discloses that a DNA binding domain as claimed in instant claim 4 are about amino acids #100 to 300 of the p53. The '676 patent, note for example the cover page, teach that most of mutations are located in amino acids #100 to 300 of the p53, where the nucleic acid sequences encodes a DNA binding domain. For claim 5, the evolutionary conserved regions of the nucleic acid are highly mutated. As for claims 6, and 7, the '676 patent discloses at column 5, lines 37-61,

> Mutant p53 genes or gene products can also be detected in body samples, such as, serum, stool, or other body fluids, such as urine and sputum. The same techniques discussed above for detection of mutant p53 genes or gene products in tissues can be applied to other body samples. By screening such body samples, a simple early diagnosis can be achieved for many types of cancers. In addition, the progress of chemotherapy or radiotherapy can be monitored more easily by testing such body samples for mutant p53 genes or gene products.
>
> The method of the present invention for diagnosis of neoplastic tissue is applicable across a broad range of tumors. These include lung, breast, brain, colorectal, bladder, mesenchyme, prostate, liver as well as stomach tumors. In addition the method may be used in leukemias and osteosarcomas. It thus appears that the p53 gene has a role in the development of a broad range of tumors. The methods of diagnosis of the present invention are applicable to any rumor in which p53 has a role in tumorigenesis. The diagnostic method of the present invention is useful for clinicians so that they can decide upon an appropriate course of treatment. For example, a tumor displaying loss of both p53 alleles suggests a more aggressive therapeutic regimen than a tumor displaying loss of only one p53 allele.

Therefore, it would have been obvious and motivated for one of ordinary skill in the art to use the instantly claimed invention by detecting mutations in nucleotide sequences, especially at the conserved regions of p53 since as prognostic factor along with node status for whether one should be treated more aggressively with adjuvant treatment after the initial surgery. The claimed invention would have been practiced

with a reasonable expectation of success because Allred et al., unequivocally teach p53 mutational status along with the node status for breast cancer patients are very important factor deciding who should receive more aggressive adjuvant chemotherapy.

Claims 1, 3, and 10 are rejected under **35 U.S.C. 103(a)** as being unpatentable over Allred et al., J Natl Cancer Inst. 1993 Feb 3;85(3):200-6 in view of US 5527676 A of record (the effective filing date of 1989), further in view of Hedrum et al., of record, Biotechniques. 1994 Jul;17(1):118-9, 122-4, 126-9..

The claimed invention is interpreted as drawn to method for prognostication of recurrence of breast cancer and providing guidance for treating breast cancer based on status of p53 mutation along with node status (base claim 1) as drawn to method for prognostication of cancer based on status of p53 mutation (base claim 3) wherein the detection is done by computer software and other automation device.

Note what Allred et al., and the '676 patent teach above.

Neither Allred et al., nor the '676 patent teach that the nucleic acid mutation detection is done by automated system.

However, Hedrum et al., teach that automated sequencing using "a robotic workstation and a laser fluorescent electrophoresis unit had been known before the effective filing date of the instant application.

Therefore, it would have been obvious and motivated for one of ordinary skill in the art to use the instantly claimed invention by detecting mutations in nucleotide sequences, especially at the conserved regions of p53 using more less labor intensive

automatic system of Hedrum et al., since as prognostic factor along with node status for whether one should be treated more aggressively with adjuvant treatment after the initial surgery. The claimed invention would have been practiced with a reasonable expectation of success because Allred et al., unequivocally teach p53 mutational status along with the node status for breast cancer patients are very important factor deciding who should receive more aggressive adjuvant chemotherapy.

Claims 1, 2, and 19 are rejected under **35 U.S.C. 103(a)** as being unpatentable over Allred et al., J Natl Cancer Inst. 1993 Feb 3;85(3):200-6 in view of US 5527676 A of record (the effective filing date of 1989), further in view of Hollstein et al., of record (1991, Science, vol. 253, pages 49-53).

The claimed invention is interpreted as drawn to method for prognostication of recurrence of breast cancer and providing guidance for treating breast cancer based on status of p53 mutation along with node status, wherein the detection is done by the specific mutation listed in claim 19.

Note what Allred et al., and the '676 patent teach above.

Neither Allred et al., nor the '676 patent teach that the specific nucleic acid mutation in the instant claim 19.

However, Hollstein et al., teach at Fig. 1, for example, that Arg at position 249 as recited in the instant claim 19 is very common in all cancers, and Arg to Ser at 249.

Therefore, it would have been obvious and motivated for one of ordinary skill in the art to use the instantly claimed invention by detecting mutations in nucleotide sequences, especially at the conserved regions of p53, especially those mutational hot spots of domains II, III, IV, and V, more specifically at position 249 since as prognostic factor along with node status for whether one should be treated more aggressively with adjuvant treatment after the initial surgery. The claimed invention would have been practiced with a reasonable expectation of success because Allred et al., unequivocally teach p53 mutational status along with the node status for breast cancer patients are very important factor deciding who should receive more aggressive adjuvant chemotherapy.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642

MISOOK YU
PATENT EXAMINER